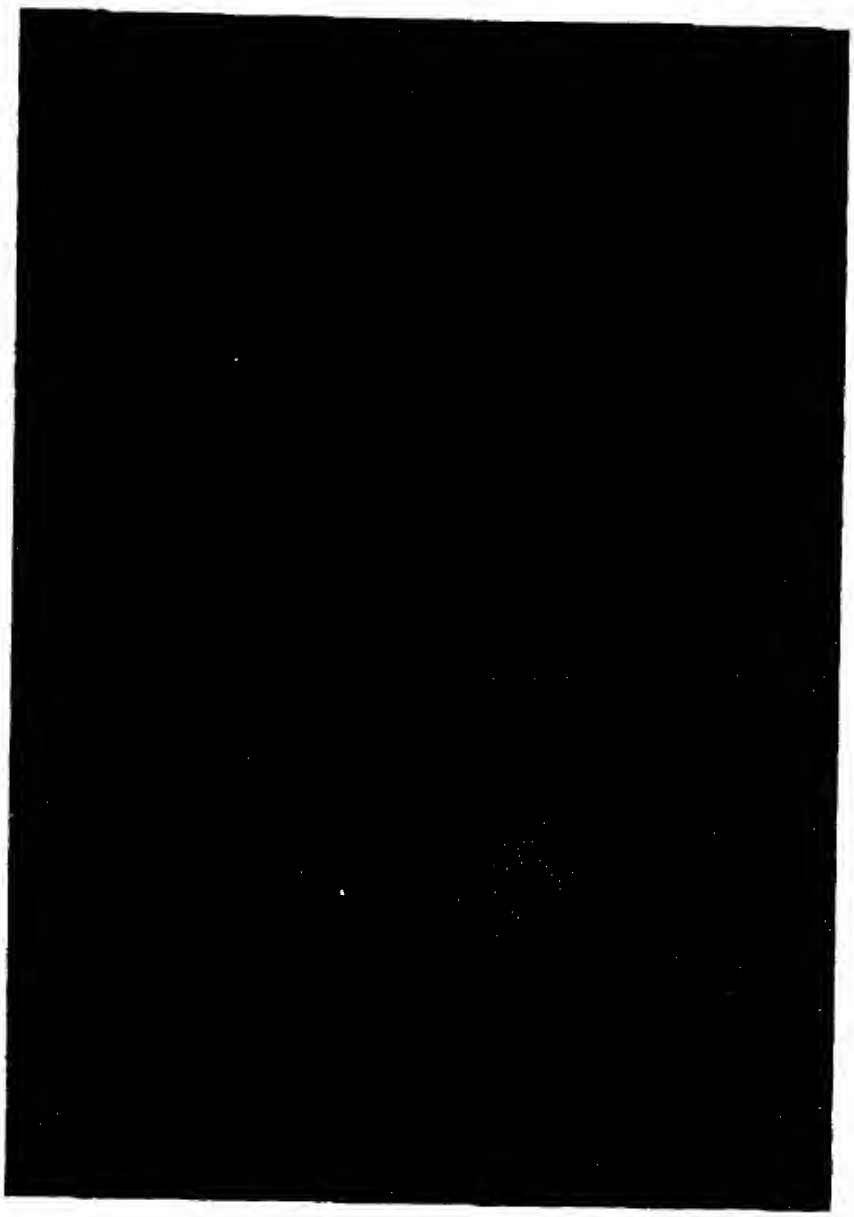

Fig. 1

```
HS-HMC-Dis3      0 ------------------------------MLKSKTFLKKTRAGGVMKIVKEHYLRDDIGCGAPGCAACG-
MM-hmc-Dis3      0 ------------------------------MLRSKTFLKKTRAGGVVKIVREHYLRDDIGCGAPACSACG-
CE-Q17632-Dis3   0 ----------------------MDLNVKQSGIHSVALHTTYFQNRSGKVYKRAEERYLRNDLSCGLAQCGTCK-
SP-P37202-Dis3   0 ----------------MSTVSGLKRPQSSEKNHRDRVFVRATRGKVQKVVREQYLRNDIPCQSRACPLCRS
SC-Q08162-Dis3   0 ----------MSVPAIAPRRKRLADGLSVTQKVFVRSRNGGATKIVREHYLRSDIPCLSRSCTKCPQ
MM-LOBO          0 ------------------------------------------------------------
HS-LOBO          0 ------------------------------------------------------------
CE-Q09568-LOBO   0 ------------------------------------------------------------
SP-Z99259        0 ------------------------------------------------------------
SC-P24276-SSD1   0 MSKNSNVNNNRSQEPNNMFVQTTGGGKNAPKQIHVAHRRSQSELTNLMIEQFTLQKQLEQVQAQQQQLMA
SC-P39112        0 ----------MVVRRKVHVLLIARSFHSVTPCFRVTTRGKRQRSKSKQQAKVELDHTRELDNDQA
                           |---------|---------|---------|---------|---------|---
                           1         11        21        31        41        51        61

HS-HMC-Dis3     40 -----GAHEGPALEPQPQ--DPASSVCPQPHYLLPDTNVLLDQIDVLEDP-AIRNVIVLQTVLQEVRNRS
MM-hmc-Dis3     40 -----GAHAGPALELQPR--DQASSLCPWPHYLLPDTNVLLHQIDVLEHP-AIRNVIVLQTVMQEVRNRS
CE-Q17632-Dis3  51 -----DFGTNPLLKIEN----PVRNAKVGRHALIVDSTSLIRFYDLPDSS-LLRDLIVTQTVWEGVKAKA
SP-P37202-Dis3  55 KLPKDSRGNVLEPILSEK--PMPLEK-FGHHYLIPDSNIFYHCIDALEHPNNFFDVIILQTVFSEISSKS
SC-Q08162-Dis3  57 IVVPDAQNELPKFILSDS--PLELSAPIGKHYVVLDTNVVLQAIDLLLENPNCFPDVIVPQIVLDEVRNKS
MM-LOBO          0 ------------------------------------------MNHPDYKLNLRSPGTPRGVSSVV
HS-LOBO          0 ------------------------------------------------------------
CE-Q09568-LOBO   0 ------------------------------------------MPFRVKTTPTTKAKPYV
SP-Z99259        0 -----MDLKPNIRRKEKR-NLLKGEAALEKKGSIDRKTKNKAYPSTTHDPHQNDDSNIPGLGSGLLERI
SC-P24276-SSD1  70 QQQQLAQQTGQYLSGNSGSNNNHFTPQPPHPHYNSNGNSPGMSAGGSRSRTHSRNNSGYYHNSYDNNNNSN
SC-P39112       55 TETVVDRSVGPEKDIESIN-KDFLQRTKGLEPDIELKQLPQIKQEFNQRYKDRYVKPSEDWYVNSWRSLT
                           |---------|---------|---------|---------|---------|---
                           71        81        91        101       111       121       131
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Fig. 2a

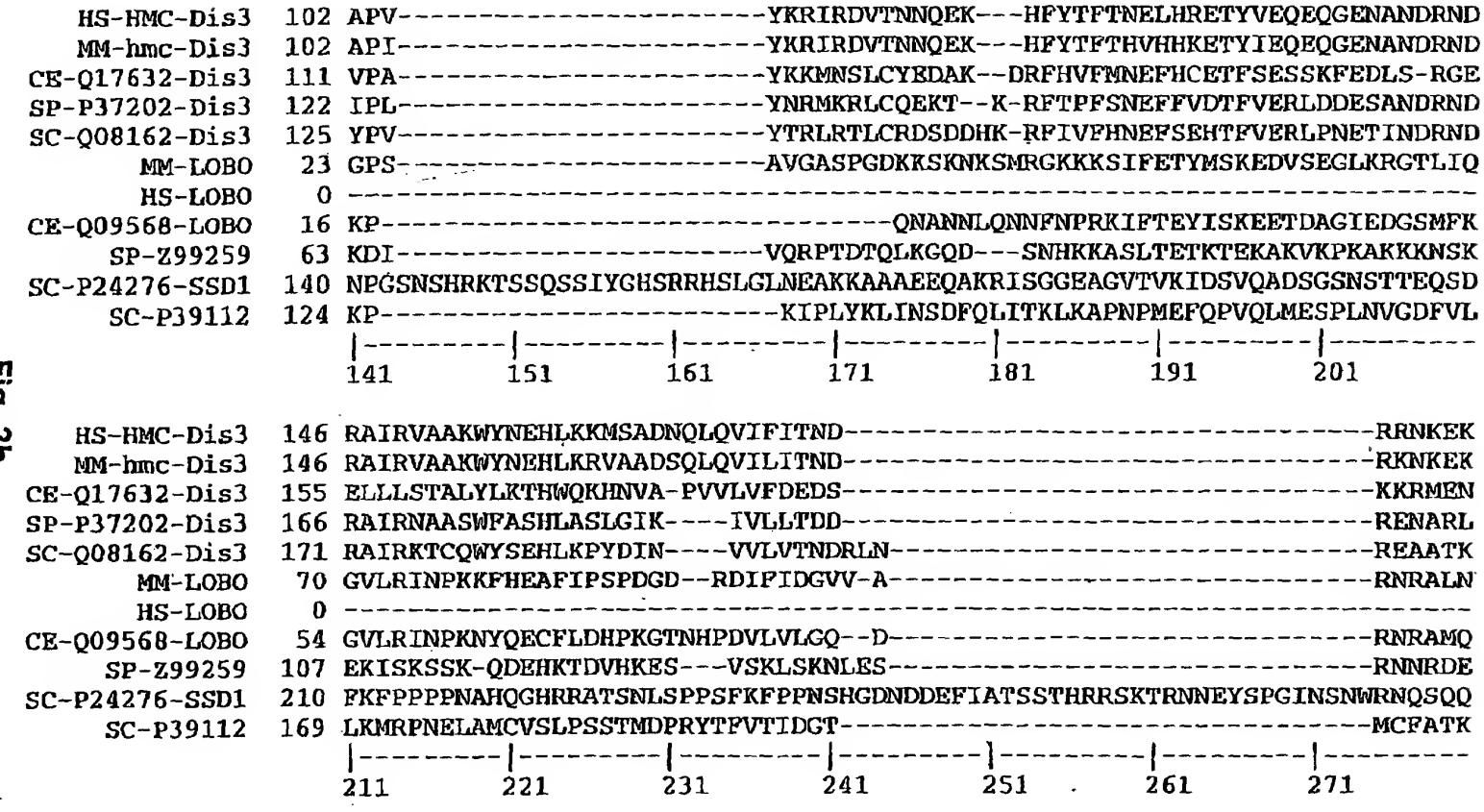

Fig. 2b

02/64511

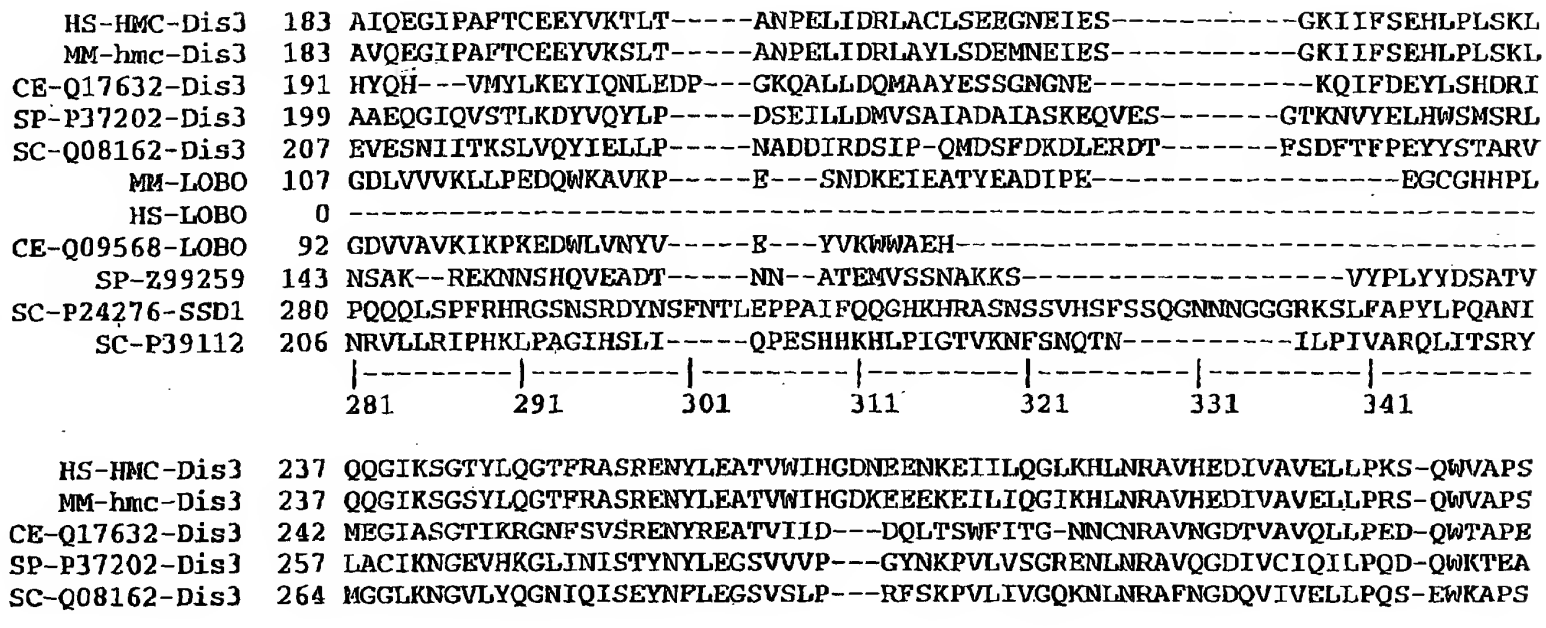

Fig. 2c

09/641,211

```
HS-LOBO          0 ------------------------------------------------------------
CE-Q09568-LOBO 120 -K--KG----------------------DRN------SGKTD------NNSPNK----TEKRCLRNE-IQDNGV
   SP-Z99259   185 KKGLKSGTLFKGTLRI-LENHR-SAFACM---EDIPDFYVDGPIARNRAFHNDVVIVEPVMNN-DSPTEK
SC-P24276-SSD1 350 PELIQEGRLVAGILRVNKKNRSDAWVSTDG--ALDADIYICGSKDRNRALEGDLVAVELLVVDDVWESKK
   SC-P39112   261 PAQISKLAWKDLPITTKKLQLLHRSLQN----YMGPWQIPFFTLVGLVQKLDLNKALDDKNGINYLTSL
                    |---------|---------|---------|---------|---------|---------|
                   351       361       371       381       391       401       411

 HS-HMC-Dis3    306 S----------------VVLHDEGQN-----EEDVEKEEEREQMLKTAVSEKMLK----------
 MM-hmc-Dis3    306 S----------------VVLDDEGQN-----EDDVEKDEEERELLLKTAVSEKMLR----------
CE-Q17632-Dis3  307 KKIRLRDVEEY-----VKTADDMGN-----EDEENDDENDE--PKAKKSKKMTV----------
SP-P37202-Dis3  323 EEIAD----------------DDED---VVVSTAAEPDSAR--INDLELITKRN--AH----------
SC-Q08162-Dis3  330 SIVLDSEHFDVNDNPDIEAGDDDDNMESSSNTTVISDKQRRLLAKDAMIAQRSKKIQ----------
   MM-LOBO      217 D----------------------------TRGLSEKSLQKSAKVVYILEKKHSRA----------
   HS-LOBO        0 ------------------------------------------------------------
CE-Q09568-LOBO  152 T----------------------------SDEVPDSCLITIGAIVHILEKKHFRV----------
   SP-Z99259    249 SNFLQNG----VEK--VKIKDHDD-----ELGGAMEHLERLEIKSVASFKGDS--R----------
SC-P24276-SSD1  418 EKEEKKRRKDASMQHDLIPLNSSDDYHNDASVTAATSNNFLSSPSSSDSLSKDDLSVRRKRSSTINNDSD
   SC-P39112    326 VN---N----------YHTVNDTP-----INSPTPVSTYWAIMQQQESNLWGEIHLN----------
                    |---------|---------|---------|---------|---------|---------|
                   421       431       441       451       461       471       481
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Fig. 2d

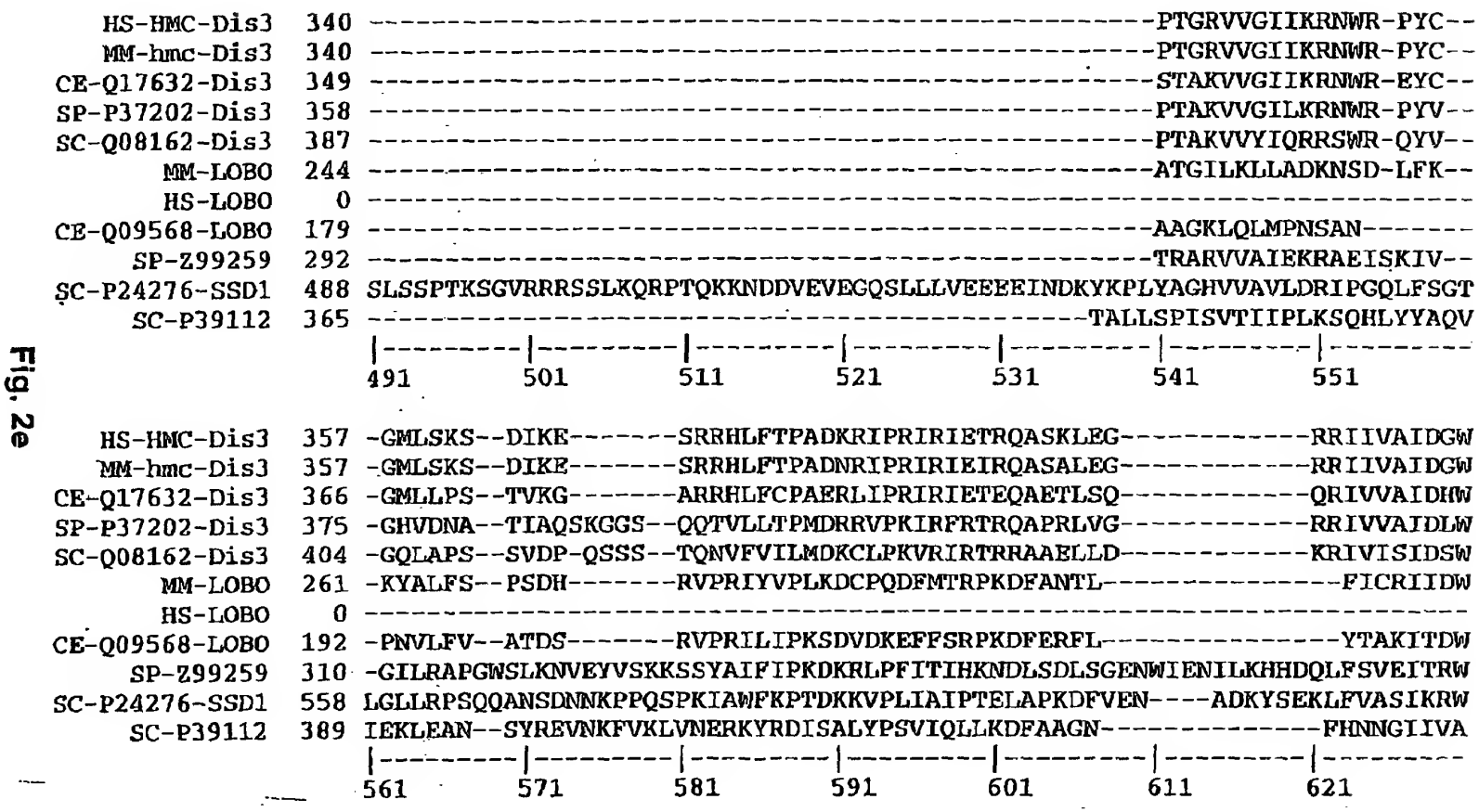

Fig. 2e

09/647211

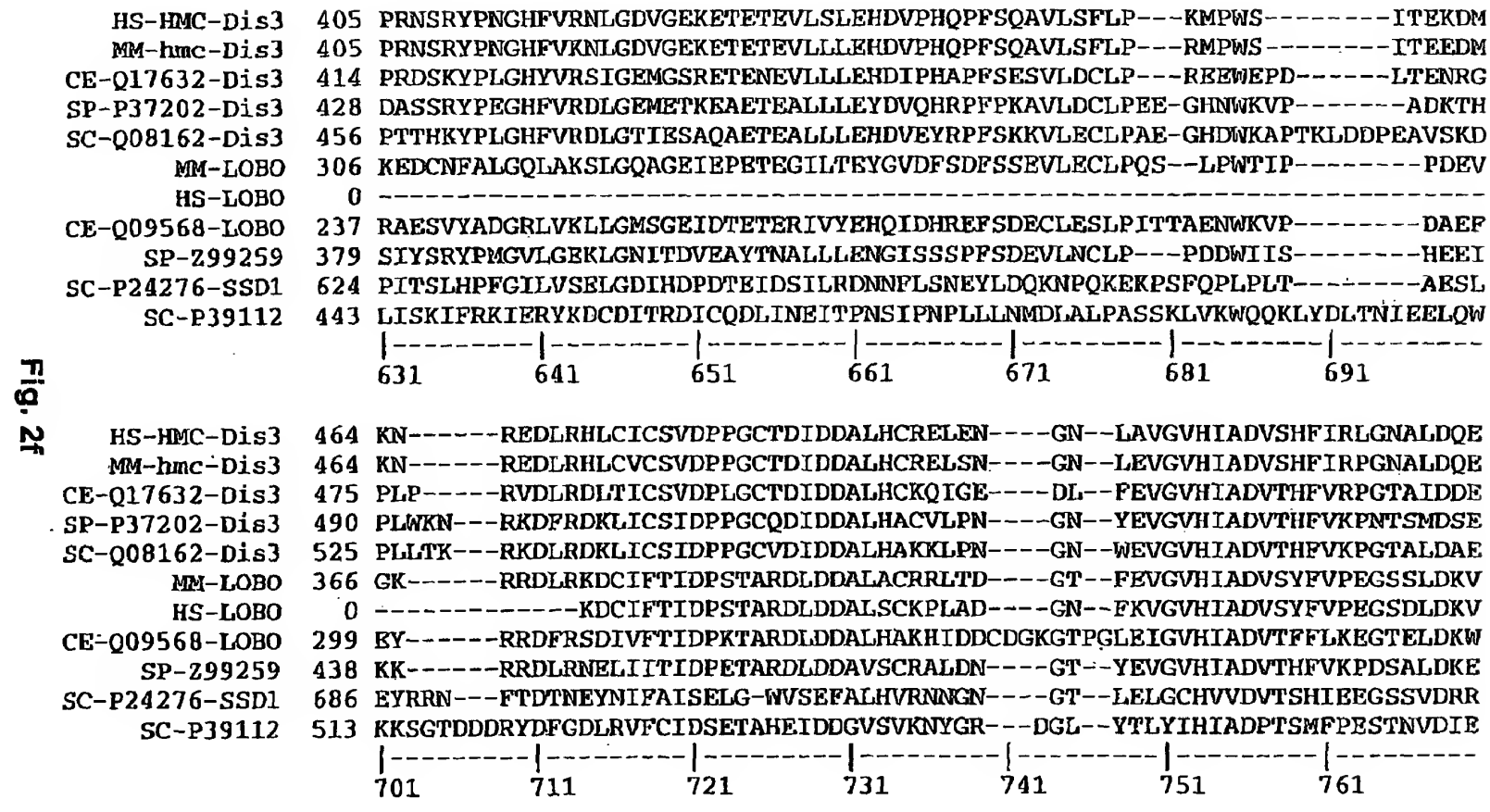

Fig. 2f

07/041111

```
HS-HMC-Dis3      522 ----------SARRGTTVYLCEKRIDMVPELLSS--NLCSLKCDVDRLAFSCIWEMNHNA----------EILK
MM-hmc-Dis3      522 ----------SARRGTTVYLCEKRIDMVPELLSS--NLCSLRSNVDRLAFSCIWEMNHNA----------EILK
CE-Q17632-Dis3   534 ----------AALRGTTVYLCDRRIDMLPCLLSS--NLCSLRGEEERYAFSCIWTMTSSA----------DIQS
SP-P37202-Dis3   551 ----------AASRGTTVYLVDKRIDMLPMLLGT--DLCSLRPYVERFAFSCIWEMDENA----------NIIK
SC-Q08162-Dis3   586 ----------GAARGTSVYLVDKRIDMLPMLLGT--DLCSLKPYVDRFAFSVIWELDDSA----------NIVN
MM-LOBO          424 ----------AAERATSVYLVQKVVPMLPRLLCE--ELCSLNPMTDKLTFSVIWKLTPEG----------KILE
HS-LOBO           51 ----------AAERATSVYLVQKVVPMLPRLLCE--ELCSLNPMSDXLTFSVIWTLTPEG----------KILD
```

Fig. 2g

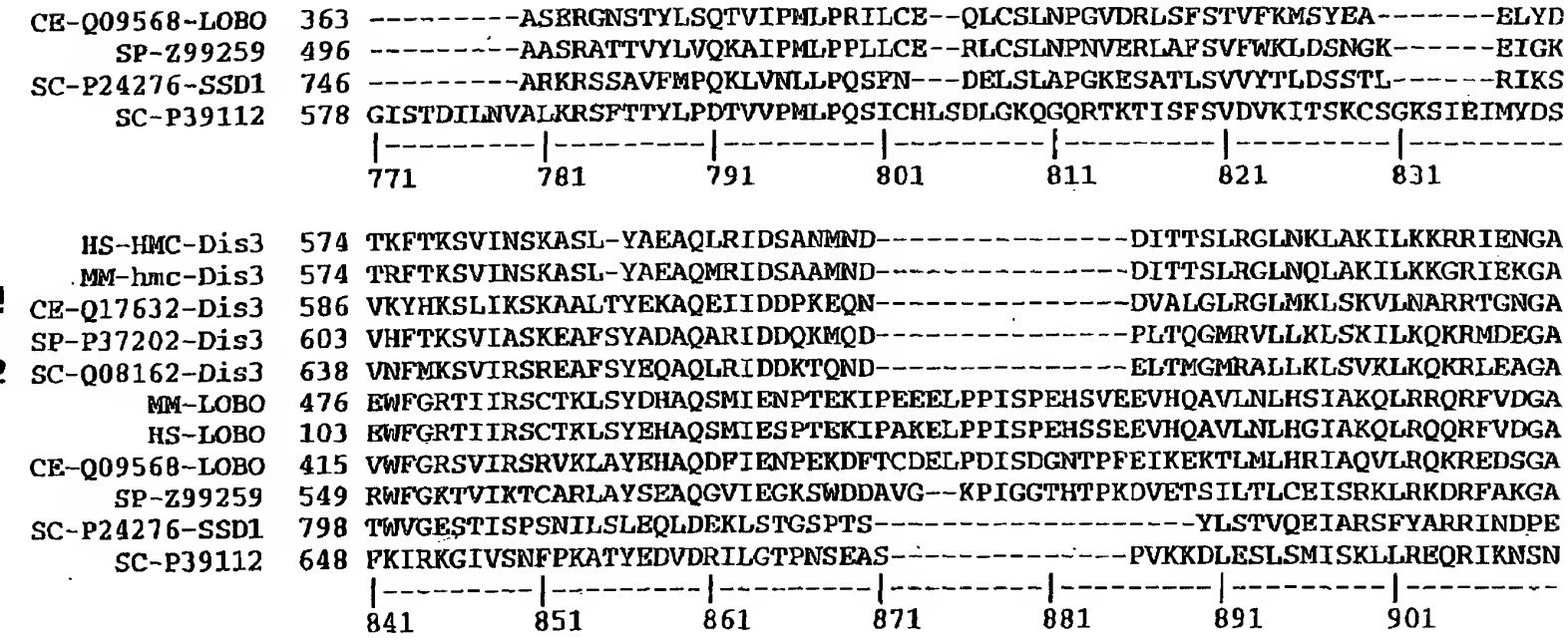

Fig. 2h

09/647311

```
HS-HMC-Dis3      628 LTLSSPEVRFHMDSETHDPIDLQTKELRETNSMVEEFMLLANISVAKKIHEEFSEHALLRKHPAPPPSNY
MM-hmc-Dis3      628 LTLSSPEIRFHMDSETHDPIDLQTKELRETNSMVEEFMLLANISVAKKIHEEFSEHALLRKHPAPPPSNY
CE-Q17632-Dis3   641 LTLASSEVRFDMDWESRTPKKVMEKQHLDTHSMVEEFMLLANISVAEKILEEYPDCALLRRHPVPLKESY
SP-P37202-Dis3   658 LNLASPEVRIQTDNETSDPMDVEIKQLLETNSLVEEFMLLANISVAQKIYDAFPQTAVLRRHAAPPLTNF
SC-Q08162-Dis3   693 LNLASPEVKVHMDSETSDPNEVEIKKLLATNSLVEEFMLLANISVARKIYDAFPQTAMLRRHAAPPSTNF
MM-LOBO          546 LRLDQLKLAFTLDHETGLPQGCHIYEYRDSNKLVEEFMLLANMAVAHKIFRTFPEQALLRRHPPPQTKML
HS-LOBO          173 LRLDQLKLAFTLDHETGLPQGCHIYEYRESNKLVEEFMLLANMAVAHKIHRAFPEQALLRRHPPPQTRML
CE-Q09568-LOBO   485 LRIELPRLKFALDEDK-KPQGVSIYEIKDSNKLVEEFMLLANMEVAKKIAENFPEHALLRNHPPPKEKMI
SP-Z99259        617 VEINSTELKFQLDEYG-MPNKCEVYEQTDANHLIEEFMLLANRSVAEHISKNFSNNSLLRRHASPKEKQI
SC-P24276-SSD1   849 ATLLPTLSLLESLDDEKVKVDINILDRTLGFVVINEIKRKVNSTVAEKIYTKLGDLALLRRQMQPIATKM
SC-P39112        704 AVIFGEGFNKGLVMLN----ADSEGELTEVTFSDQEETLSTILVSEMMILANTLTGRYPAEN------KI
                     |---------|---------|---------|---------|---------|---------|
                     911       921       931       941       951       961       971

HS-HMC-Dis3      698 EILVKAARS-RNLEIKTDTAKSLAESLDQAESPTFPYLN--TLLRILATRCMMQAVYFCSGMD-------
MM-hmc-Dis3      698 DILVKAAKS-KNLQIKTDTAKSLADSLDRAESPDFPYLN--TLLRILATRCMMQAVYFCSGMD-------
CE-Q17632-Dis3   711 KPLVEAARH-RGFEIIVESGKGLADSLNRCVDKKNPMLN--RLLRMLTTRCMTQAVYFSAGKDGFSDIKL
SP-P37202-Dis3   728 DSLQDILRVCKGMHLKCDTSKSLAKSLDECVDPKEPYFN--TLLRILTTRCMLSAEYFCSGTFAP------
SC-Q08162-Dis3   763 EILNEMLNTRKNMSISLESSKALADSLDRCVDPEDPYFN--TLVRIMSTRCMMAAQYFYSGAYSY------
MM-LOBO          616 SDLVEFCDQ-MGLPMDVSSAGALNKSLTKTFGDDKYSLARKEVLTNMYSRPMQMALYFCSGMLQD-----
HS-LOBO          243 SDLVEFCDQ-MGLPVDFSSAGALNKSLTQTFGDDKYSLARKEVLTNMCSRPMQMALYFCSGLLQD-----
CE-Q09568-LOBO   554 KDVAEQCAR-IGFPLDGRTSGLLSTSLRKYQGKSRLDMCIRQVISSLTIKPMQQAKYFCT--FEM------
SP-Z99259        686 NEFCHFLKS-MNFDFDASSSAAFNASMVRLRSTFNEELV--ELFENMAVRSLNRAEYFCTGDFGEK-----
SC-P24276-SSD1   919 ASFRKKIQN-FGYNFDTNTADELIKGVLKIKDDDVRVGI------EILLFKTMPRARYFIAGKVD-------
SC-P39112        764 GGVFRCYKQ---LPLGEVAQQQYDSMITSTKKGIFPKLK------DIVKLSSLLNSSFYTGRPFR------
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Fig. 2i

09/647377

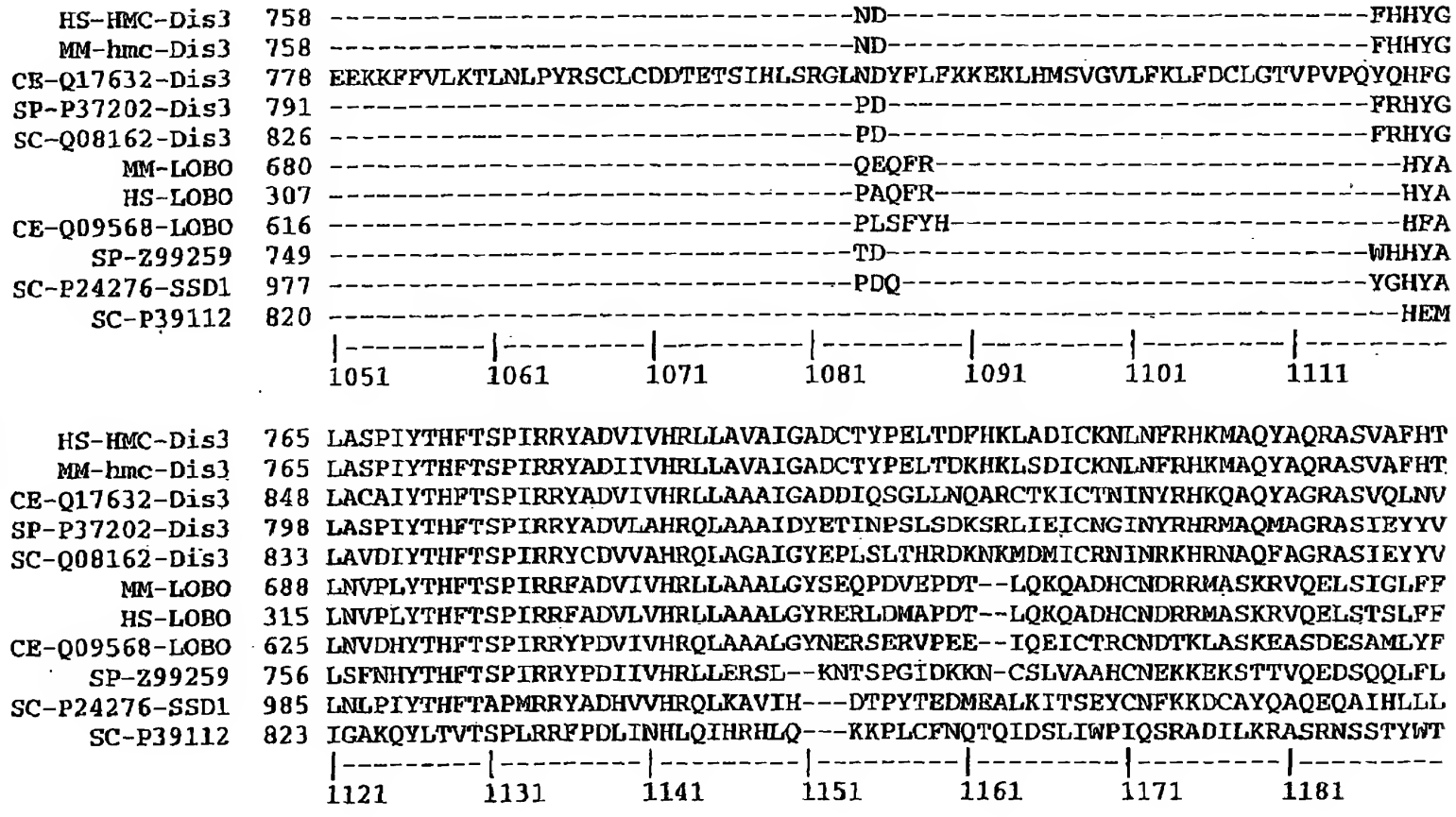

Fig. 2i

```
HS-HMC-Dis3     835 QLFFKSKG------IVSEEAYILFVRKNAIVVLIPKYGLEGTVFPEEKDKPNPQLI----------
MM-hmc-Dis3     835 QLFFKSKG------IVSEEAYILFVRKNAIVVLIPKYGLEGTVFPEEKDKPKPRLA----------
CE-Q17632-Dis3  918 VRYFKGK-------VETCEGFVMGVRNNGIQVFVPKYGLESIIVLQTSAASG--TT----------
SP-P37202-Dis3  868 GQALKGG-------VAEEDAYVIKVFKNGFVVFIARFGLEGIVYTKSLSSVLEPN----------
SC-Q08162-Dis3  903 GQVMRNN-------ESTETGYVIKVFNNGIVVLVPKFGVEGLIRLDNLT--EDPNS----------
MM-LOBO         756 AVLVKESG------PLESEAMVMGVLNQAFDVLVLRFGVQKRIYCNALALRSYSFQ----------
HS-LOBO         383 AVLVKESG------PLESEAMVMGILKQAFDVLVLRYGVQKRIYCNALALRSHHFQ----------
CE-Q09568-LOBO  693 GVFIHQTG------PMKCQAVVLGVMDLSFDVLIVEYGVVKRVYVDKMKR---DFN----------
```

Fig. 2k

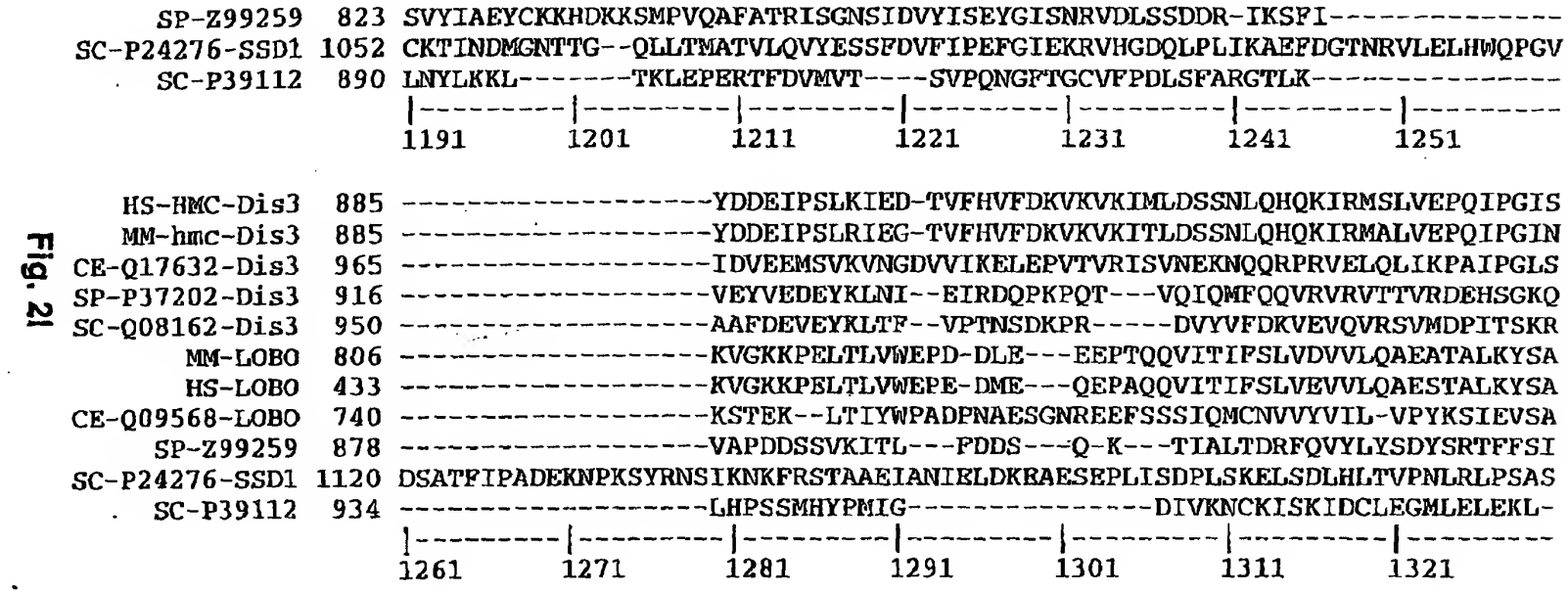

Fig. 21

09/647011

```
HS-HMC-Dis3      935 IPTDTS------NMDLNGPKKKKMKLGK----------
MM-hmc-Dis3      935 IPPNVA------DKALTAPGGKKRKLEK----------
CE-Q17632-Dis3  1016 V-----------DFDLSSSEG----LGL----------
SP-P37202-Dis3   962 K----V------QITLVY----------
SC-Q08162-Dis3   994 K----A------ELLLK----------
        MM-LOBO  853 ILKRPG----------LEKASDEEPED----------
        HS-LOBO  480 ILKRPGTQGHLGPEKEEESDGEPEDSSTS----------
CE-Q09568-LOBO   788 TIVRPS----LEQRNILKSTLKDMKETGSTILQ----------
        SP-Z99259  919 R-----------CSLVSLN----------
SC-P24276-SSD1  1190 DNKQNALEKFISTTETRIENDNYIQEIHELQKIPILLRAEVGMALPCLTVRALNPFMKRV
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Fig. 2m

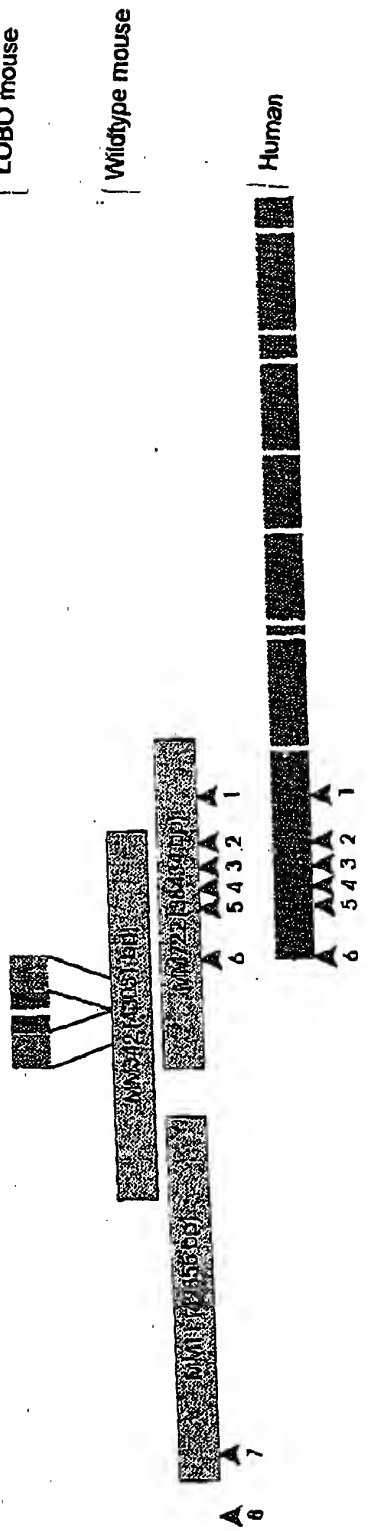


Fig. 3

LOBO
WT
Proliferative zone
Hypertrophic chondrocytes
Proliferative zone
Hypertrophic chondrocytes

Fig. 4

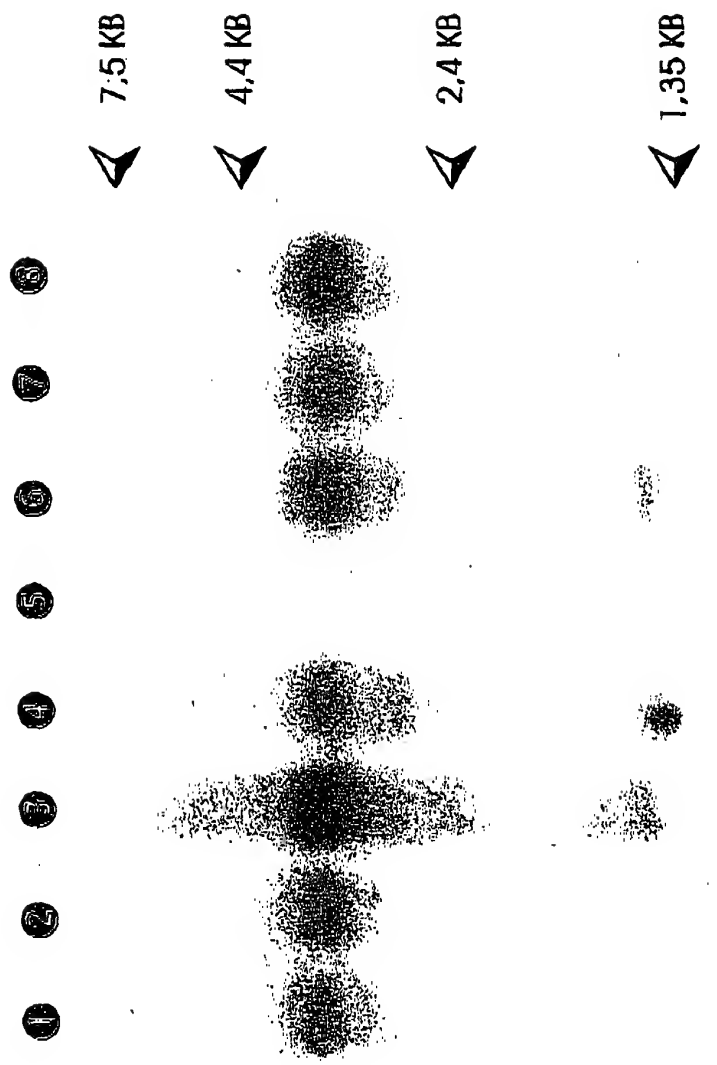
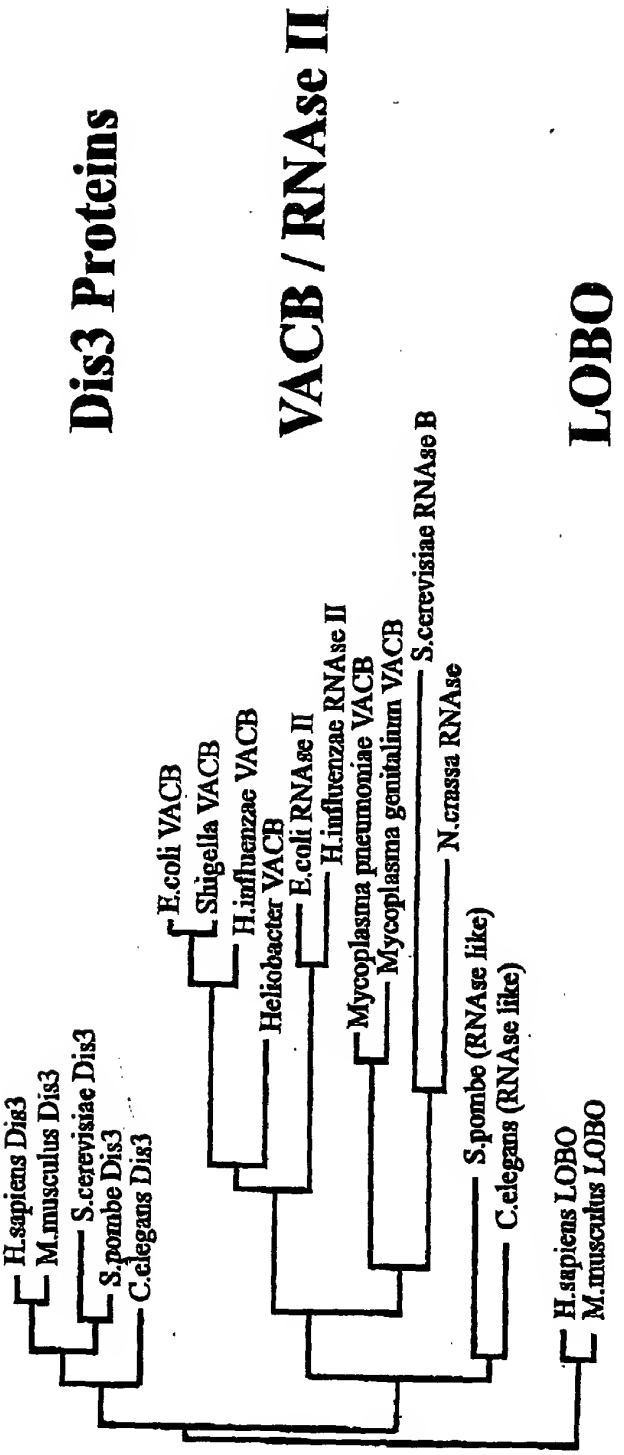


Fig. 5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VACB / RNAse II
LOBO
H.sapiens Dis3
M.musculus Dis3
S.cerevisiae Dis3
S.pombe Dis3
C.elegans Dis3
E.coli VACB
Shigella VACB
H.influenzae VACB
Helicobacter VACB
E.coli RNAse II
H.influenzae RNAse II
Mycoplasma pneumoniae VACB
Mycoplasma genitalium VACB
S.cerevisiae RNAse B
N.crassa RNAse
S.pombe (RNAse like)
C.elegans (RNAse like)
H.sapiens LOBO
M.musculus LOBO

Fig. 6

Fig. 7

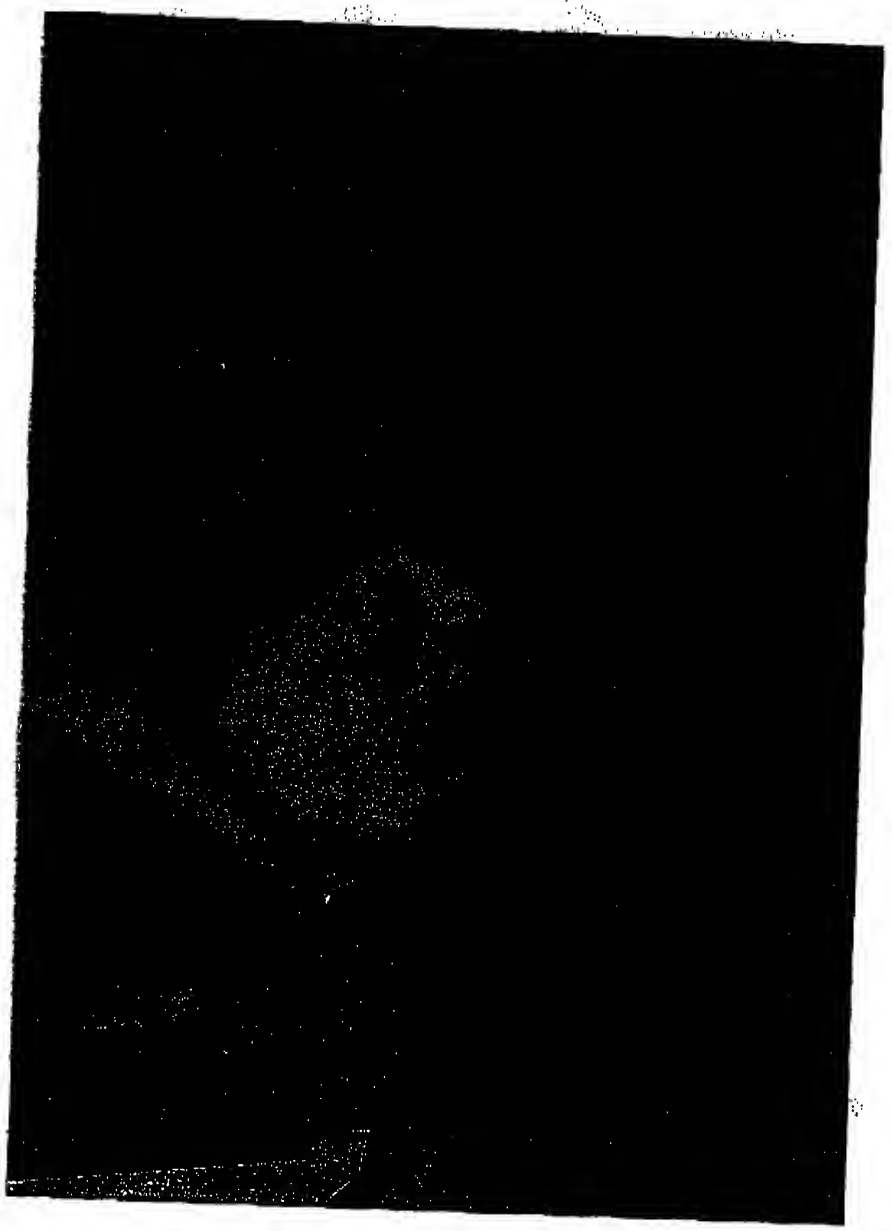
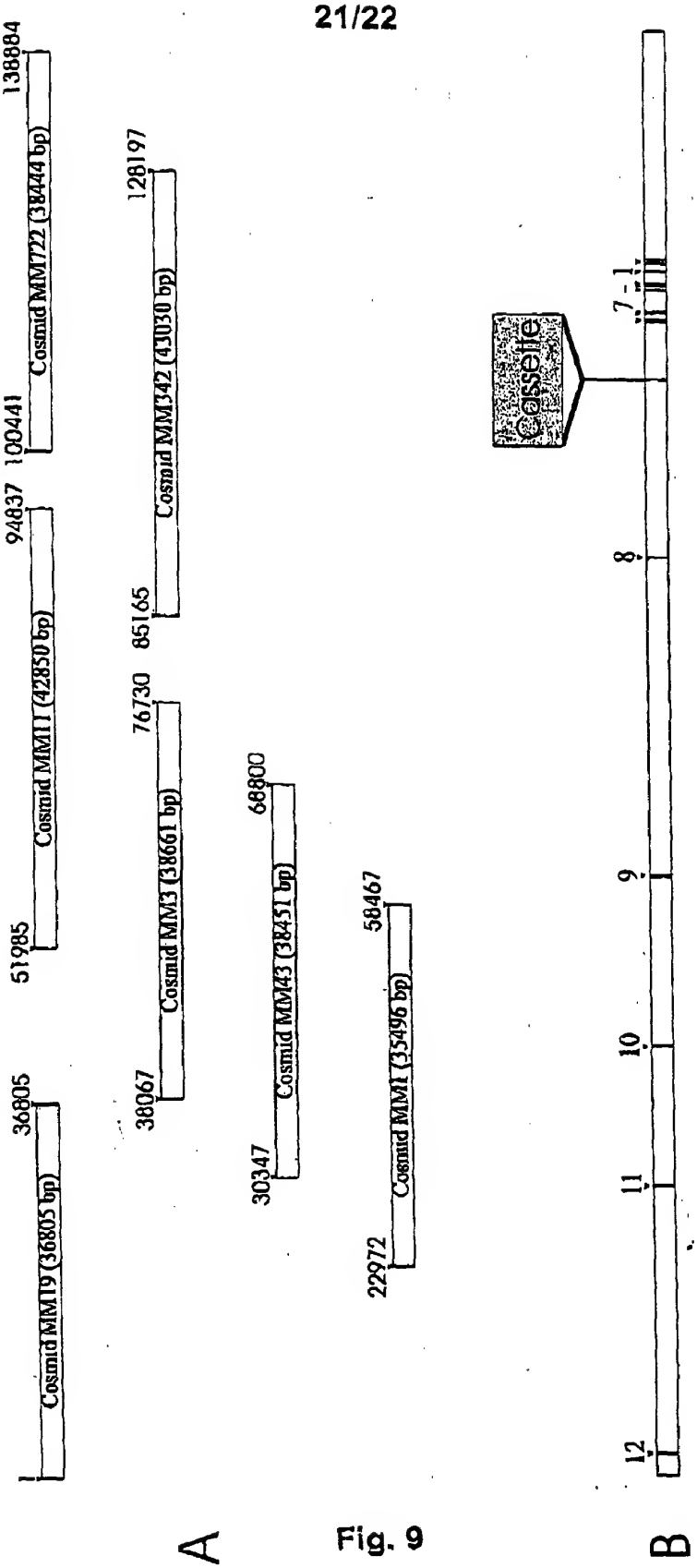


Fig. 8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30347
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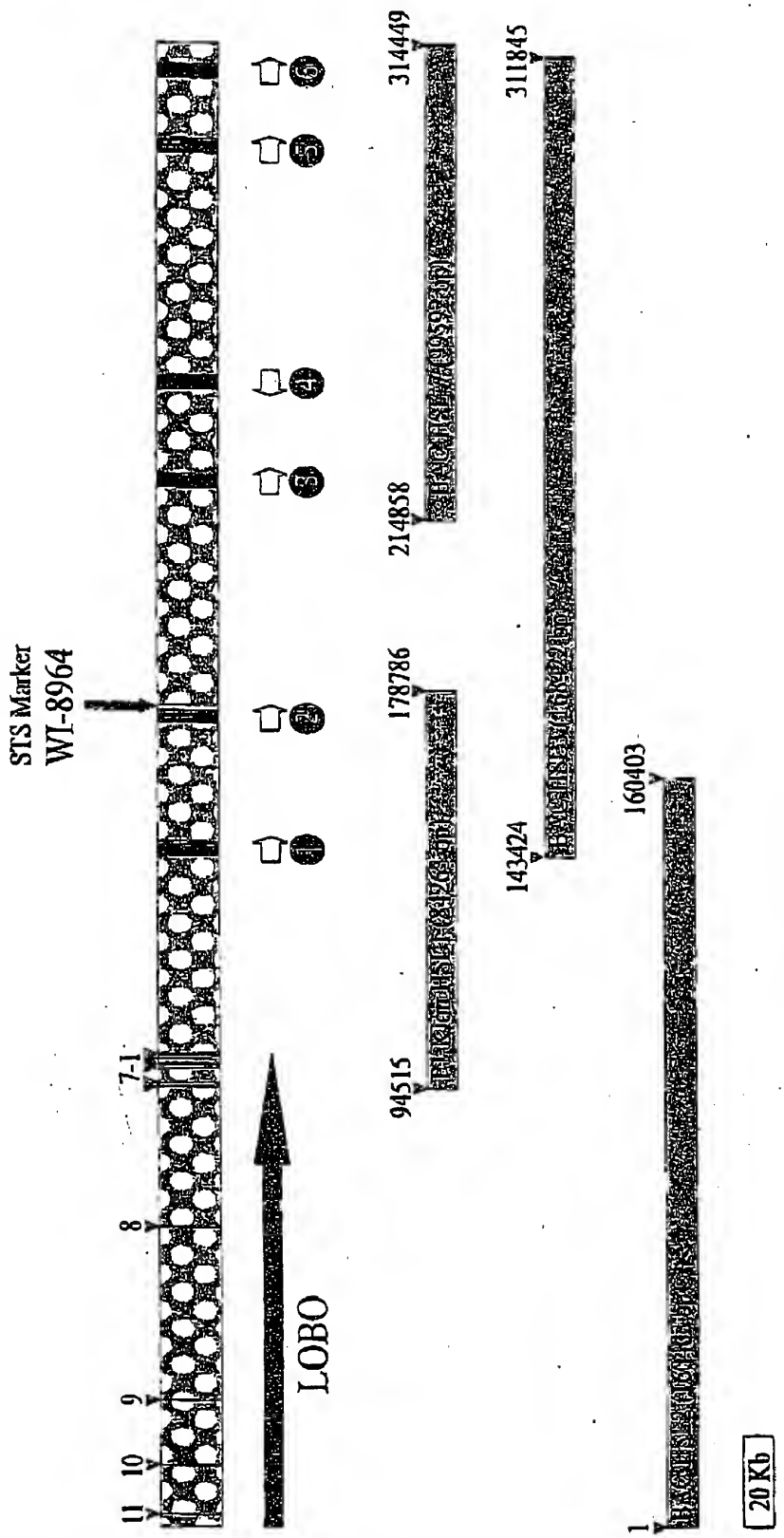
B
12
11
10
9
8
7
1
cassette

Fig. 9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1
20 Kb

Fig. 10